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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/525,121	02/18/2005	John Cumming	06275-441US1 100741-1P US	2965

26164 7590 11/01/2007

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EXAMINER	
O DELL, DAVID K	

ART UNIT	PAPER NUMBER
1625	

MAIL DATE	DELIVERY MODE
11/01/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/525,121	CUMMING ET AL.	
	Examiner	Art Unit	
	David K. O'Dell	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *18, February 2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-8, 11 are pending in the current application.

2. This application is a 371 of PCT/SE03/01287 filed 08/19/2003, which claims priority to Swedish application 0202483-4 filed 08/21/2002.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 3 recites the limitation "S(O)n(C1-4 alkyl)" while the parent claim (claim 1) recites" S(O)mC1-4 alkyl". There is insufficient antecedent basis for the limitation "n" in claim.

Claim Rejections - 35 USC § 102

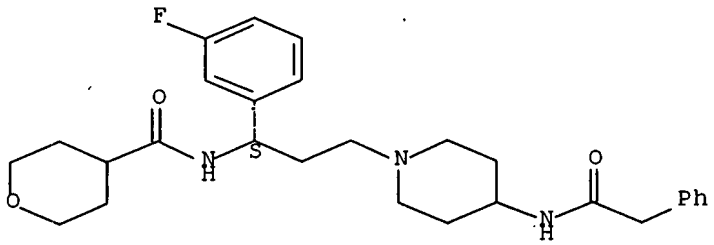
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

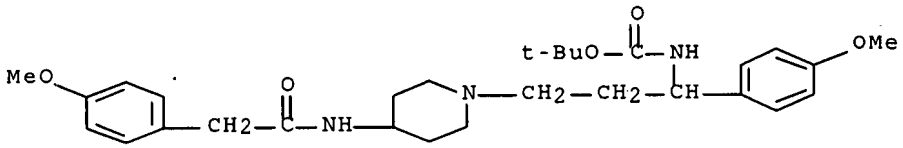
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1, 3, 4, 7, 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Armour et. al. EP1013276. Armour reveals many anticipatory species:

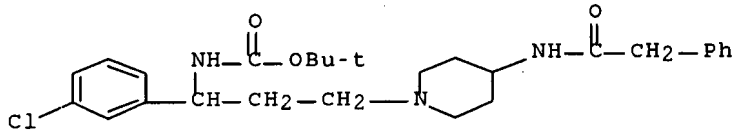
```
RN   277745-16-1  CAPLUS
CN   2H-Pyran-4-carboxamide, N-[(1S)-1-(3-fluorophenyl)-3-[4-
     [(phenylacetyl)amino]-1-piperidinyl]propyl]tetrahydro- (9CI)  (CA INDEX
     NAME)

Absolute stereochemistry.
```



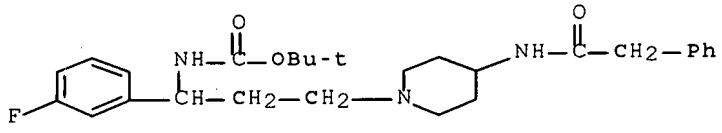
RN 277745-58-1 CAPLUS
CN Carbamic acid, [1-(4-methoxyphenyl)-3-[4-[[(4-methoxyphenyl)acetyl]amino]-1-piperidinyl]propyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



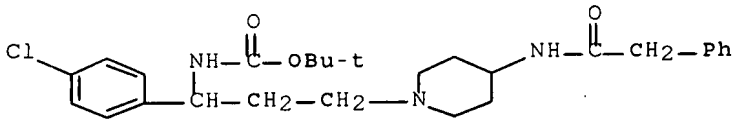
RN 277745-59-2 CAPLUS
CN Carbamic acid, [1-(3-chlorophenyl)-3-[4-[(phenylacetyl)amino]-1-piperidinyl]propyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RN 277745-60-5 CAPLUS
CN Carbamic acid, [1-(3-fluorophenyl)-3-[4-[(phenylacetyl)amino]-1-piperidinyl]propyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

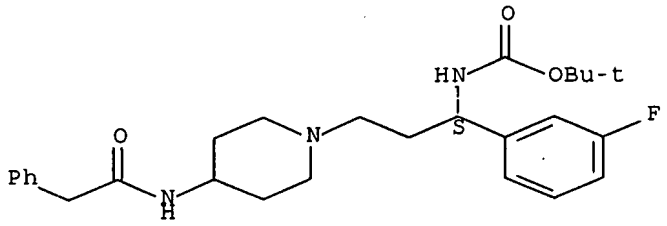


RN 277745-61-6 CAPLUS
CN Carbamic acid, [1-(4-chlorophenyl)-3-[4-[(phenylacetyl)amino]-1-piperidinyl]propyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



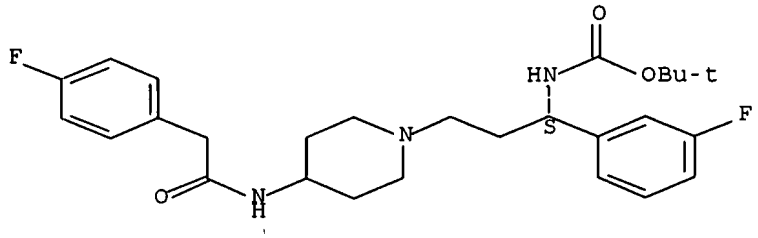
RN 277745-62-7 CAPLUS
CN Carbamic acid, [(1S)-1-(3-fluorophenyl)-3-[4-[(phenylacetyl)amino]-1-piperidinyl]propyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 277745-63-8 CAPLUS
CN Carbamic acid, [(1S)-1-(3-fluorophenyl)-3-[4-[[(4-fluorophenyl)acetyl]amino]-1-piperidinyl]propyl]-, 1,1-dimethylethyl ester
(9CI) (CA INDEX NAME)

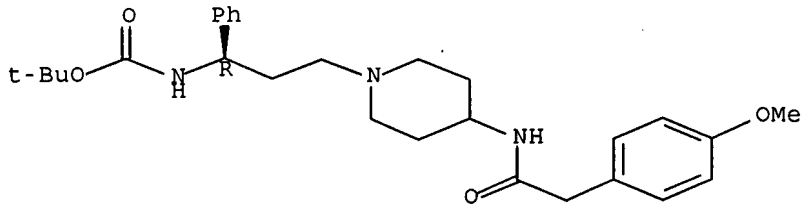
Absolute stereochemistry.



RN 277745-64-9 CAPLUS
CN Carbamic acid, [(1R)-3-[4-[[(4-methoxyphenyl)acetyl]amino]-1-

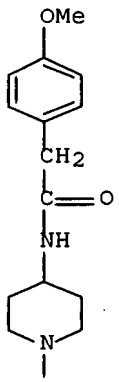
piperidinyl]-
1-phenylpropyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

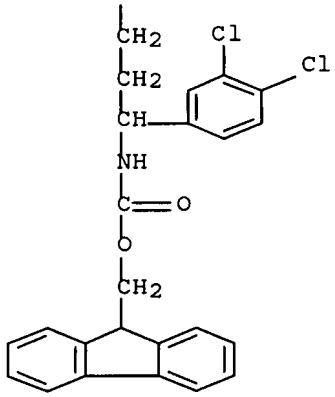


RN 277745-65-0 CAPLUS
CN Carbamic acid, [1-(3,4-dichlorophenyl)-3-[4-[[(4-
methoxyphenyl)acetyl]amino]-1-piperidinyl]propyl]-, 9H-fluoren-9-
ylmethyl
ester (9CI) (CA INDEX NAME)

PAGE 1-A



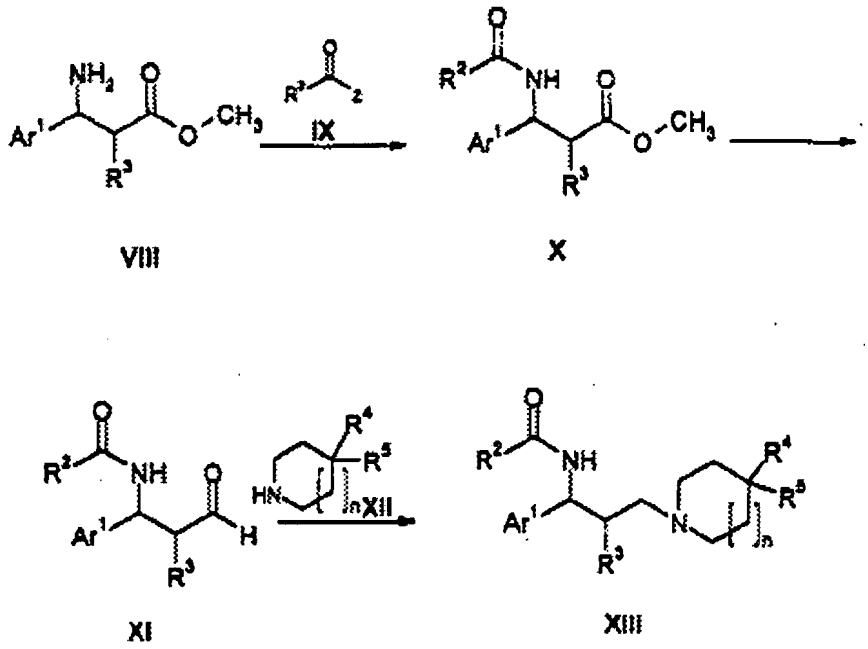
PAGE 2-A



These compounds can be constructed from the instant claims when R6 is phenyl(C1-2)alkyl substituted variously, R2 is phenyl substituted variously (as per claim 3), R3-R5 are H, R1 is various alkoxy.

These materials were prepared (claim 7) in the same manner as applicant's claim (XXI – XXII):

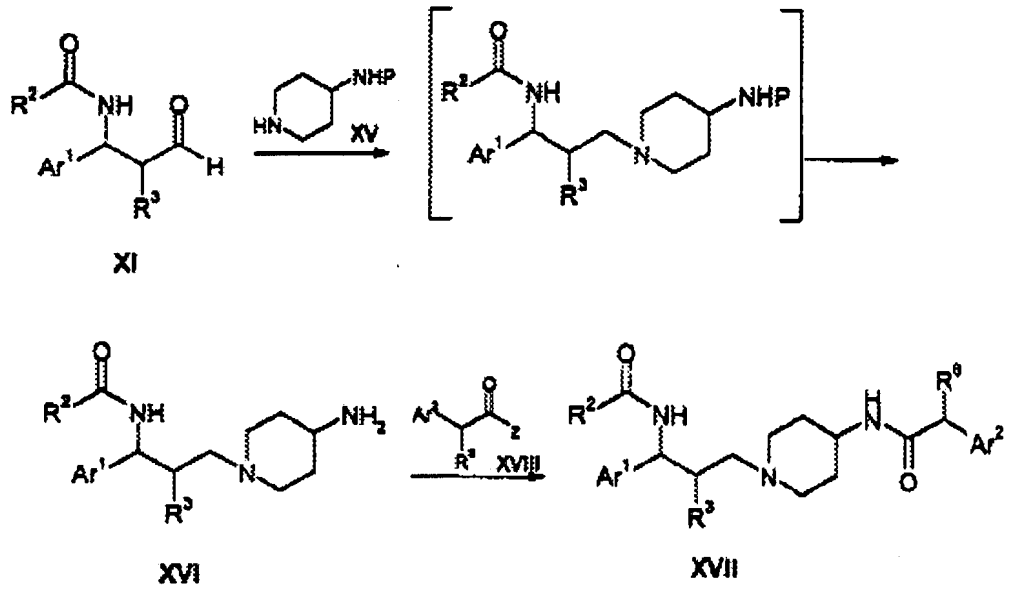
Synthesis II



n = 0 or 1

[0127] Compounds of formula **X** may be prepared by coupling the amino acid derivative of formula **VIII** with an acid (Z = OH) or acid derivative (e.g., Z = Cl) of formula **IX** using conventional amide bond forming techniques as described in synthesis I. R^3 may be hydrogen or OH. In the case of R^3 = OH methylation to $R^3 = OCH_3$ may be performed using, for example, iodomethane and silver oxide in acetonitrile at reflux. Compounds of formula **XI** may be prepared by reduction of compounds of formula **X**, according to the method described in synthesis I. Reductive alkylation of the amine of formula **XII**, with the aldehyde of formula **XI**, according to the method described in synthesis I, may provide the compounds of formula **XIII**.

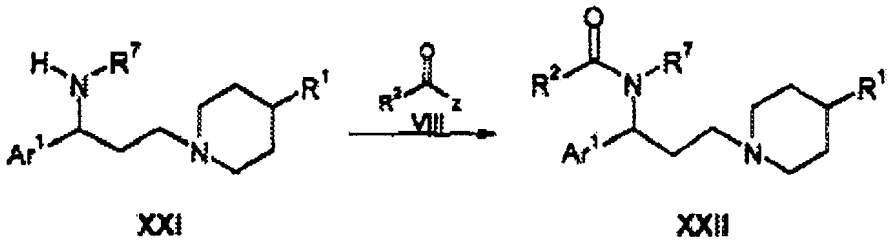
Synthesis III



[0129] Compounds of the general formula **XVI** may be prepared by the reductive alkylation of an appropriate amine of formula **XV**, where P is a suitable protecting group (preferably trifluoroacetyl), with an aldehyde of formula **XI**. The reaction may be carried out in the presence of an excess of suitable reducing agent (e.g. sodium triacetoxyborohydride) in a protic solvent system (acetic acid in 1,1,1-trichloroethane), at room temperature.

[0130] Subsequent removal of the nitrogen protecting group in a "one-pot procedure" may be achieved using, for example, an excess of aqueous sodium hydroxide in a solvent such as ethanol at room temperature for 1 hour to provide the compound of formula **XVI**.

[0131] Compounds of formula **XVII** may be prepared by coupling the amine of formula **XVI** with an acid (Z = OH) or acid derivative (e.g., Z = Cl) of formula **XVIII** using conventional amide bond forming techniques as described in synthesis I.



[0134] Compounds of formula **XXII** may be prepared by coupling the amine derivative of formula **XXI** with an acid (Z = OH) or acid derivative (e.g., Z = Cl) of formula VIII using conventional amide bond forming techniques as described in synthesis I.

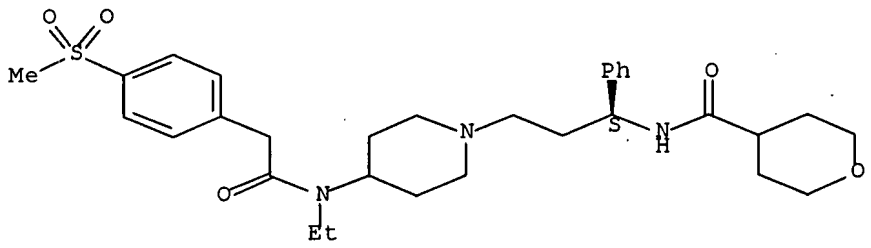
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language

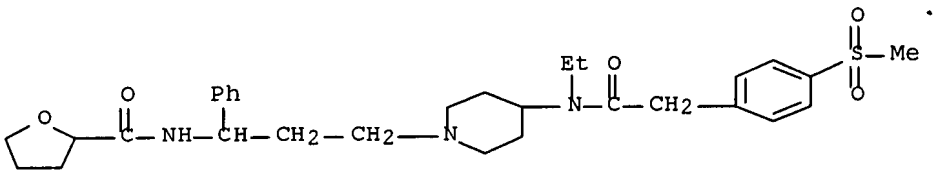
5. Claims 1, 3-8 are rejected under 35 U.S.C. 102(e) as being anticipated by Burrows et. al. WO 2002070479.

Burroughs reveals two anticipatory species:

```
RN   458529-58-3  CAPLUS
CN   2H-Pyran-4-carboxamide, N-[(1S)-3-[4-[ethyl[[4-
     (methylsulfonyl)phenyl]acetyl]amino]-1-piperidinyl]-1-
     phenylpropyl]tetrahydro- (9CI)  (CA INDEX NAME)

Absolute stereochemistry.
```




```
RN   458529-30-1  CAPLUS
CN   2-Furancarboxamide, N-[3-[4-[ethyl[[4-
(methylsulfonyl)phenyl]acetyl]amino]-
     1-piperidinyl]-1-phenylpropyl]tetrahydro- (9CI)  (CA INDEX NAME)
```



These compounds can be constructed from the instant claims when R6 is benzyl substituted with SO2Me, R2 is phenyl substituted variously (as per claim 3), R3-R5 are H, R1 is C5 or C6 alkoxy.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain compounds it does not reasonably provide enablement for the scope of compounds bearing the extensive list of substituents. The compounds that are enabled are as follows:

R2 should be limited to: phenyl bearing a F atom as an optional substituent; R3 R3a R4 R4a should be limited to H, R6 must be phenyl that must bear a sulfone.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(A) The breadth of the claims: The claims are very broad encompassing all heterocycles, carbocycles and other groups bearing multiple substitutions of unascertainable structure. **(B) The nature of the invention:** This is a chemical invention requiring the synthesis of compounds and such compounds should have activity at a specific chemokine receptor. **(D) The level of one of ordinary skill**: One of ordinary skill is a practicing organic/medicinal chemist. **(C) The state of the prior art: (E) The level of predictability in the art: (F) The amount of direction provided by the inventor, (G) The existence of working examples, and (H) The quantity of experimentation needed to make or use the invention:** Each one of the factors (**C, E-H**) will be discussed in light of the scientific literature when such a factor is being directly pointed to a large capital letter referring to the aforementioned Wands factor will be placed directly after such a remark or explication. The examiner will first consider the Markush structure I of claim 2, and discuss the limitations inherent to the chemistry required to prepare the compounds. The only route given is that reproduced in Figure 1.

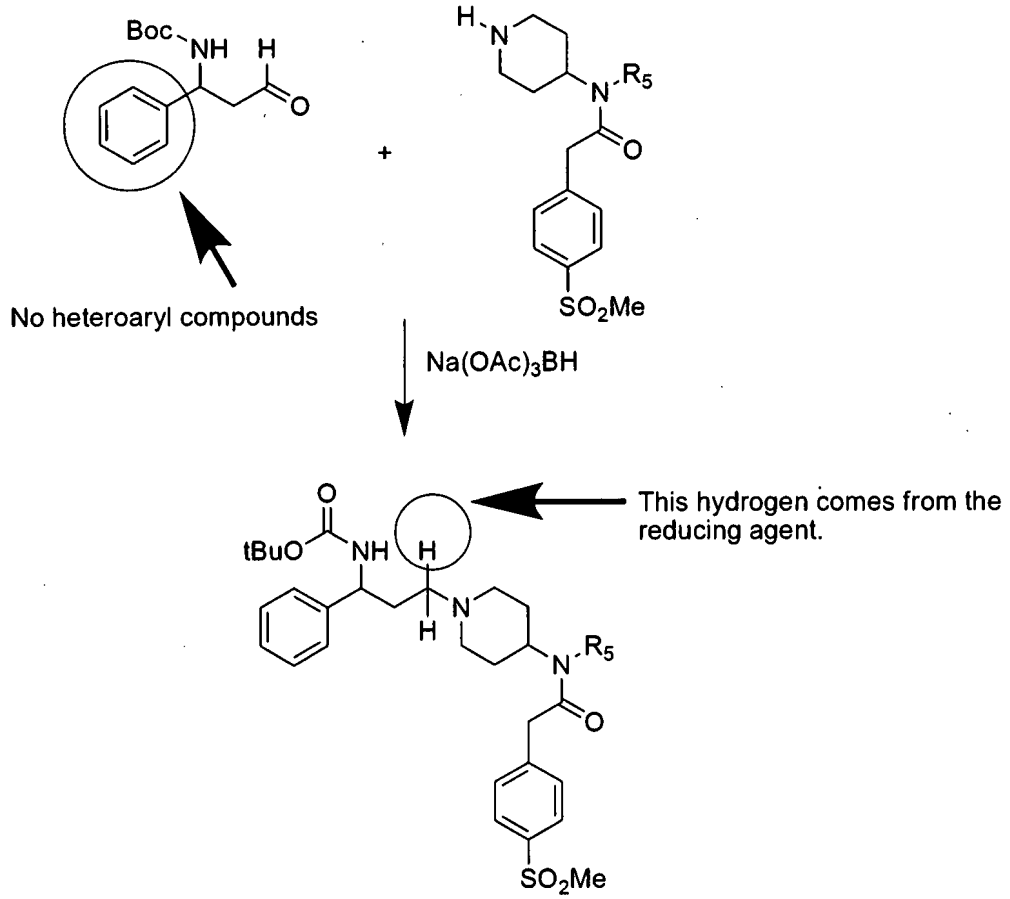


Figure 1. Selected Synthetic Intermediates

These syntheses rely on reductive amination of aldehydes. The definition R2 requires numerous specialized aldehydes. Where can one purchase or find the directions to prepare the vast array of aldehydes, needed for the scope of the claims? The specification cites several obscure publications including Onischu Romanian patent 75530 and Zahran et. al. *International Journal of Chemistry* 1993, 4(3) 61-68 (abstract only). These publication were not provided to the examiner, however upon obtaining them the examiner notes that these publications do deal with issues germane to the synthesis of the compounds of the instant claims. In particular Zahran

deals with the synthesis of pyranocoumarins. The examiner would like clarification of the exact page and line in these references relevant to the compounds of the instant case.

As per MPEP:

> A key issue that can arise when determining whether the specification is enabling is whether the starting materials or apparatus necessary to make the invention are available. In the biotechnical area, this is often true when the product or process requires a particular strain of microorganism and when the microorganism is available only after extensive screening. The Court in In re Ghiron, 442 F.2d 985, 991, 169 USPQ 723, 727 (CCPA 1971), made clear that if the practice of a method requires a particular apparatus, the application must provide a sufficient disclosure of the apparatus if the apparatus is not readily available. The same can be said if certain chemicals are required to make a compound or practice a chemical process. In re Howarth, 654 F.2d 103, 105, 210 USPQ 689, 691 (CCPA 1981).

According to the U.S. Court of Customs and Patent Appeals in *In re Argoudelis, De Boer, Eble, and Herr* 168 USPQ 99 at 101, "[o]rdinarily no problem in this regard arises since the method of preparing almost all starting materials can be set forth in writing if the materials are not already known and available to the workers in the art, and when this is done the specification is enabling to the public". *In re Argoudelis, De Boer, Eble, and Herr* 168 USPQ 99 at 104, "it is essential that there be no question that, *at the time an application for patent is filed,* (emphasis in original) the invention claimed therein is fully capable of being reduced to practice (i.e., that no technological problems, the resolution of which would require more than ordinary skill and reasonable time, remain in order to obtain an operative, useful embodiment)." That is not the situation here. Rather we find very little direction as to how the many required staring materials with these vast substituents are to be obtained. Where may the directions to prepare or buy them be found? **(F)**

In re Howarth, 210 USPQ 689, (claimed derivatives of clavulanic acid not enabled by specification lacking information of how prepare the clavulanic acid or directions to reference materials containing such information), *Ex parte Schwarze* 151 USPQ 426 (where starting

material is not known to art as of date of filing application, there must be included a description of preparation thereof to enable one skilled in this art to carry out applicant's invention), *Ex parte Moersch* 104 USPQ 122 (claims to process for the production of (1)-y1-p-nitrophenyl-2-dichloracetamindo-propane-1,3-diol not enabled because of failure to describe source or method of obtaining starting compound; although starting compound is identified by means of appropriate name and by structural formula).

Even if such materials were obtainable, the chemistry used to construct the compounds is not applicable to the scope claimed and currently no methods exist for the scope claimed. The limitations of synthetic chemistry is readily apparent as stated in the preface to a recent treatise:

> "Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually

> implies will be able to appraise such work.....Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious)....." Dorwald F. A. *Side Reactions in Organic Synthesis*, 2005, Wiley: VCH, Weinheim pg. IX of Preface. **(E)**

The use of Sodium triacetoxyborohydride during reductive amination would reduce the C-X bond in halogentated alkyls to the alkanes (Hutchins, R.O. et. al. *J. Org. Chem.* **1977**, *42*, 82-91). Relevant to R5. It is not at all clear to the examiner how these "halogens" could be introduced into the compounds. It is also clear that this reagent is the source of one hydrogen atoms. Are new reagents being created for reductive amination that will produce compounds where R4 or R4a is other than H? (See Figure 1)

Many of the compounds currently under the Markush claim could not exist but would self-polymerize instantaneously if prepared as stated by Dorwald ibid. pg. 41 "It goes without saying that a compound will decompose or oligomerize if it contains functional groups which can react with each other. Because intramolecular reactions often proceed at much higher rates than their intermolecular variants, functional group incompatibilities may arise unexpectedly, involving groups which would not react intermolecularly..." **(C & E)**

(H) While these chemical limitations are significant, perhaps more significant are the limitations related to the activity of the compounds as CCR5 ligands. The medicinal chemistry in this area is relatively well-developed and many limitations are well known in the art. In a study of similar compounds Thoma, et. al. "Orally Bioavailable Competitive CCR5 Antagonists" *Journal of Medicinal Chemistry* **2004**, *47*, 1939-1955, made the following statement, about substituents on the phenyl rings:

> "First we explored a few analogues of the highly potent CCR5 antagonist 1a with a cyano substituent in different positions of the benzyl group (Table 1). The 3-substituted compound 1c was found to be even more potent than unsubstituted 1a on both human and cyno CCR5. The 2-substituted derivative 1b was significantly less potent than 1a in the human binding assay but highly inferior in the Ca2+-mobilization assay. In addition, it was found to be almost inactive on cyno CCR5. The 4-substituted derivative 1d was considerably less potent than 1c. **Compound 1e with a trimethoxybenzyl group was found to be completely inactive. These findings suggest that substituents of the benzyl group are well tolerated in the 3-position but can significantly reduce the affinity when attached to other ring positions.** Furthermore, the substitution pattern seems to affect the reactivity on human vs cyno CCR5." Pg. 1941 (**C & E**)

Thus it is clear that substitution can have a very pronounced impact on the active pharmacophore, and a choice of the wrong substituent or **too many substituents** gives compounds with no activity. The claims here may have up to 5 substituents for R2 and R6. All the working examples have only one substituent on the phenyl ring, no synthesis has been given for these compounds bearing all these groups. We have not been given any information in regard to the molecular determinants of receptor affinity for the compounds of the instant case. **(F & G)** In fact the only information we are given is in on pg. 33 of the specification reproduced here:

> (IC_{50}). The compounds of formula (I) had an IC_{50} of less than 50μM. For example: Compound 1 of Table I has an IC_{50} of 39nM (that is 39 nanoM); Compound 5 of Table I has an IC_{50} of 28nM; and, Compound 3 of Table II has an IC_{50} of 110nM.

(F) What are the important structural features for the claimed utility? We do not know for sure but based on the SAR of Thoma et. al. we know that it is very important what the identity of these substituents are. Thus it is abundantly clear that many of the compounds of claim 1, do not carry structural characteristics even remotely associated with the desired activity. As one

reviewer stated, Martin, Yvonne C. et. al. "Do Structurally Similar Molecules Have Similar Biological Activity?" *Journal of Medicinal Chemistry* **2002**, *45*, 4350-4358:

> "..... compounds that look very similar to a chemist sometimes bind in very different orientations in the protein active site, bind to a different conformation of a protein, or bind to a different protein altogether.[15] In fact, such observations are why medicinal chemists need to make so many compounds to optimize the biological activity of a structural class, even when they are designing to a biological target of known structure...(pg. 4536 column 2, line 9).....This work also shows that the biological similarity is not so strong as has previously been assumed. For example, at ≥ 0.85 Tanimoto similarity in Daylight fingerprints, **only 30% of compounds similar to an active are themselves active**."(conclusions) **(H).**

The factors outlined in *In Re Wands* mentioned above apply here, and in particular As per the MPEP 2164.01 (a): "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification , at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." It is very clear that one could not make/use this very broad invention that has no working examples in this unpredictable art without undue experimentation. **(C, E, F, G, H).** Genetech Inc Vs Nova Nordisk 42 USPQ 2d 1001 "A patent is not a hunting license. It is not a reward for search but compensation for its successful conclusion and patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1, 3-8 are rejected under 35 U.S.C. 103(a) as being obvious over Armour et. al. EP1013276 (cited on IDS) in view of Burrows et. al. WO 2001087839 (cited on IDS).

The instant claims, in particular claim 5, are drawn to compounds where R5 is ethyl and claim 6 where R6 is a benzyl sulfone.

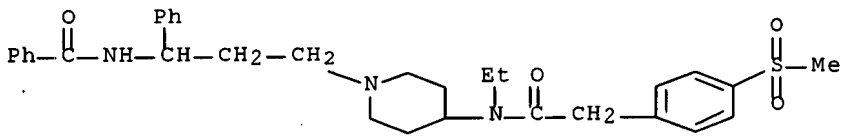
The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

Determination of the scope and content of the prior art

(MPEP 2141.01)

Armour et. al. teaches many anticipatory species, but fails to teach compounds where R5 is ethyl or R6 is a benzyl sulfone (see the 102 (b) rejection supra). Burrows teaches these modifications to the same type of chemokine receptor ligand. The compound is shown below:

```
RN   374725-05-0  CAPLUS
CN   Benzeneacetamide, N-[1-[3-(benzoylamino)-3-phenylpropyl]-4-piperidinyl]-
N-
     ethyl-4-(methylsulfonyl)-  (CA INDEX NAME)
```



Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Armor et. al. do not expressly teach the compounds of the instant case (where R5 is Ethyl and R6 is a benzyl sulfone).

Finding of prima facie obviousness

Rational and Motivation
(MPEP 2142-2143)

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to prepare the compounds of the instant case. The compounds of the claims at hand are analogs of old compounds. One of ordinary skill would be motivated to make the compounds of the invention because he would expect the compounds to have similar properties, indeed we see that these compounds have the same properties. A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of

ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary. *In re Grabiak* 226 USPQ 870, "[w]hen chemical compounds have "very close" structural similarities and similar utilities, without more a *prima facie* case may be made", *In re Deuel* 34 USPQ2d 1210, "a known compound may suggest its **analogs** or isomers, either geometric isomers (*cis* v. *trans*) or position isomers (emphasis added) (*e.g. ortho v. para*)".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claim 11 is rejected under 35 U.S.C. 112, first paragraph, for lack of enablement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the the invention as claimed. No enablement is provided for a "mediating a chemokine receptor mediated disease state". There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(B) The nature of the invention: This is medical invention requiring the treatment of a long list of diseases under the banner inflammatory disorders. **(D) The level of one of ordinary skill**: One of ordinary skill is a medical doctor. **(C) The state of the prior art (E) The level of predictability in the art; (F) The amount of direction provided by the inventor, (G) The existence of working examples, and (H) The quantity of experimentation needed to make or use the invention:** The inventor has provided no working examples of the treatment of a disease. In fact we only have one assay in the specification, directed towards CCR5. For CCR5 (a chemokine receptor embraced by the instant claims), this particular assay does not correlate well with antiviral activity:

> "The perhydro azaindole series (17–24b) provided better orientation and both 18 and 21 had comparable activity to 2 in the binding assay. Since 18 and 21 each contained four stereoisomers, the individual isomers 23a,b and 24a,b with S stereochemistry at the quaternary center were synthesized. Both 23b and 24b were as good as 2 in the CCR5 binding assay but their anti-viral activity was significantly lower. **This result clearly demonstrates that CCR5 binding affinity is not sufficient for anti-viral activity** and other features such as rate of dissociation from the receptor or some physical property might be important. **Among the fused lactams, 28 and 29 both displayed moderate CCR5 affinity, but also lacked anti-viral activity.**" Shah et. al. *Bioorganic & Medicinal Chemistry Letters* **2005**, *15*, 977–982.

Moreover, this receptor (CCR5) is a GPCR with a vast number of binding sites and conformations each of which may be associated with a distinct physiological outcome. One reviewer has summarized the situation this way (Terry Kenakin and Ongun Onaran "The ligand paradox between affinity and efficacy: can you be there and not make a difference?" *TRENDS in Pharmacological Sciences* **2002**, *23*, 275-280):

"A probabilistic model of protein conformation can be used to quantify the probability of various receptor conformations and the effect of ligand binding on those conformations. The basic idea behind the probabilistic model is that the function of a receptor protein is not assigned to particular conformations of the receptor. Instead, the function arises as a result of ligand-induced perturbation of the distribution of conformational states over the

conformational space of the receptor.....**The foregoing discussion leads to the general conclusion that if a ligand binds to the receptor, it most probably will produce a bias in the conformations of the receptor ensemble** [i.e. it will change the receptor by its presence (Fig. 3)]. Therefore, **this suggests that all ligands with macro-affinity should be extensively studied for pharmacological activities other than simple G-protein activation because various physiological activities have been defined that are mediated by conformations not necessarily related only to G-protein activation**..... "

Here we have exactly this situation, namely a ligand with affinity, but limited information about its function, which as Kenakin et. al. concluded "...the discovery of macro-affinity of a ligand for a receptor should be considered only a starting point for the optimal exploitation of a drug for therapeutic utility." By the applicant's own admission (pg. 1 of the specification), currently 16 different chemokine receptors are known (four more have since been discovered):

> Studies have demonstrated that the actions of the chemokines are mediated by subfamilies of G protein-coupled receptors, among which are the receptors designated CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CXCR1, CXCR2, CXCR3 and CXCR4.

In addition about 50 different chemokines (the endogenous ligands) are known.

Presumably to treat inflammatory diseases, one would need to antagonize an endogenous ligand, and not stimulate the receptor. There are a diverse number of these compounds:

> "A number of CC chemokines (MIP-1a, MIP-1b, RANTES, MCP-1, MCP-2, MCP-3 and MCP-4) bind CCR5 with different affnities and abilities to activate the receptor (Blanpain et al., 1999). These chemokines can be divided in two subgroups based on amino acid sequence identity (Baggiolini et al., 1994; 1997). MIP-1a, MIP-1b and RANTES form one subgroup and are full agonists, whereas MCP-1, MCP-2, MCP-3 and MCP-4 form a second subgroup which share *60% amino acid identity within the group and *30% identity with MIP-1a, MIP-1b and RANTES. MCP-3 has been reported to bind CCR5 but is unable to activate the receptor in a number of tests (Blanpain et al., 1999). MCP-2 and MCP-4 are full agonists in some tests, with MCP-4 demonstrating a reduced potency. **The diverse effects of these chemokines suggest that they interact differently with CCR5 as compared with MIP-1a, MIP-1b and RANTES. Thus, the outcome of chemokine-receptor interactions may reflect the affnity of the chemokine for a receptor and its ability to induce conformational change(s), thereby**

affecting G protein interactions." Mueller et. al. *British Journal of Pharmacology* **2002** *135*, 1033 – 1043.

No evidence supports antagonism of any chemokine. Each chemokine has unique binding sites, physiological effects, etc. The number of coupling partners associated with this GPCR is quite large, the interaction with these proteins and the subsequent signaling is poorly understood. Medical interest centers on antagonism of chemokine receptors. The evidence does support antagonism of a single chemokine, as only binding data is presented. These compounds may very well be agonists. It is very clear that undue experimentation is required. The factors outlined in *In Re Wands* mentioned above apply here, and in particular As per the MPEP 2164.01 (a): "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification , at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." It is very clear that one could not make/use this very broad invention that has no working examples in this unpredictable art without undue experimentation.

9. Claims 1 & 8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making solvates of the claimed compounds. The specification does not enable any person skilled in the art of synthetic organic chemistry to make the invention commensurate in scope with these claims. "The factors to be considered [in making an enablement rejection] have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the

predictability or unpredictability of the art, h) and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. In the present case the important factors leading to a conclusion of undue experimentation are the absence of any working example of a formed solvate, the lack of predictability in the art, and the broad scope of the claims.

g) The state of the art is that is not predictable whether solvates will form or what their composition will be. In the language of the physical chemist, a solvate of organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State Chemistry). West, Anthony R., "Solid State Chemistry and its Applications, Wiley, New York, 1988, pages 358 & 365. The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph on page 365, West (Solid State Chemistry) says, "it is not usually possible to predict whether solid solutions will form, or if they do form what is their compositional extent". Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometery of the formed solvate, i.e. if one, two, or a half a molecule of solvent added per molecule of host. In the same paragraph on page 365 West (Solid State Chemistry) explains that it is possible to make meta-stable non-equilibrium solvates, further clouding what Applicants mean by the word solvate. Compared with polymorphs, there is an additional degree of freedom to solvates, which means a different solvent or even the moisture of the air that might change the stabile region of the solvate.

h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula I as well as the presently unknown list of solvents embraced by the term "solvate". Thus, the scope is broad.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 1-8, 11 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 of copending Application No. 10/469,361. The claims are coextensive in scope. This is a provisional obviousness-type double patenting rejection.

11. Claims 1-8, 11 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of copending Application No. 10/495,405. The claims are coextensive in scope. Although the compounds of the '220 application is a salt, salts are prima facie obvious.

This is a provisional obviousness-type double patenting rejection.

Conclusion

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571) 272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Primary examiner, Rita Desai can be reached on (571)272-0684. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

RITA DESAI
PRIMARY EXAMINER
10/26/07